Quiz

Correct answer to the quiz. Check your diagnosis

Intraoral manifestation of systemic AL amyloidosis with unique microscopic presentation of intracellular amyloid deposition in striated muscles

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We report the history of a 59-year old patient with systemic AL amyloidosis of intraoral manifestation. The patient first presented with complaints about dysphagia and remarkable enlargement of the tongue with highly reduced mobility, as well as bilateral submucosal thickenings on the cheeks. Histopathological examination of the incisional biopsy of the buccal mucosa and underlying tissues revealed AL amyloidosis. The microscopic presentation was, however, unique, as the amyloid deposits were present intracellularly in the striated muscles. The subsequent bone marrow biopsy confirmed the diagnosis of primary amyloidosis/multiple myeloma – associated amyloidosis.

Key words: AL amyloidosis, amyloid, multiple myeloma, macroglossia, oral manifestation.

Introduction

Amyloidosis comprises a group of conditions characterized by either systemic or local accumulation of ultra-structurally fibrillar insoluble protein – amyloid. The deposition of amyloid occurs mainly extracellularly and, if extensive, impairs the architecture and function of tissues and organs [1]. The chemical diversity of human amyloid protein is high – until now 36 forms have been identified [2]. Upon hematoxylin and eosin staining, amyloid deposits appear as pink to red amorphous masses. Amyloid fibrils bind Congo red and when stained with this dye, deposits exhibit specific apple-green birefringence when viewed by polarization microscopy [2]. Congo red staining remains the gold standard for amyloid identification. Clinically, amyloidosis can be localized or systemic [3]. Systemic amyloidosis can further be divided into: AL amyloidosis (associated with lymphoid or plasma cell neoplasms), AA amyloidosis (associated with chronic inflammatory diseases) and hereditary amyloidosis [3, 4].

The head and neck amyloidosis is rarely observed and the precise incidence of the disease in this anatomic region remains unclear. It seems that the majority of cases of head and neck amyloidosis represent localized AL amyloidosis. Larynx is most commonly involved; however other sites, including trachea, orbit, paranasal sinuses, oro- and nasopharynx may also be affected. The involvement of larynx occurs rarely in the course of systemic amyloidosis. In contrast, amyloid-related macroglossia is most often associat-

Fig. 1. Macroglossia with a waxy surface of the dorsum of the tongue. Indentations on both margins of the tongue. Diffuse ecchymosis on the skin of the left cheek

Fig. 2. Deep indentations on the lateral margin of the tongue. Depapillation of the dorsum

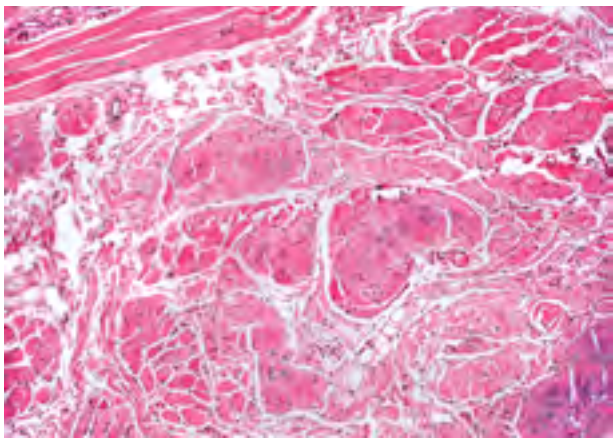

Fig. 3. From the upper left corner: the several small vessels with thickened wall are visible above and below the longitudinal section of apparently normal muscle fascicle; in the center of the specimen the muscle fascicles (cross section) are totally or partially infiltrated by amyloid; in the right lower corner homogenous deposits involve the interstitium. Amyloid deposits are focally calcified (basophilic areas; HE, original magnification 40×)

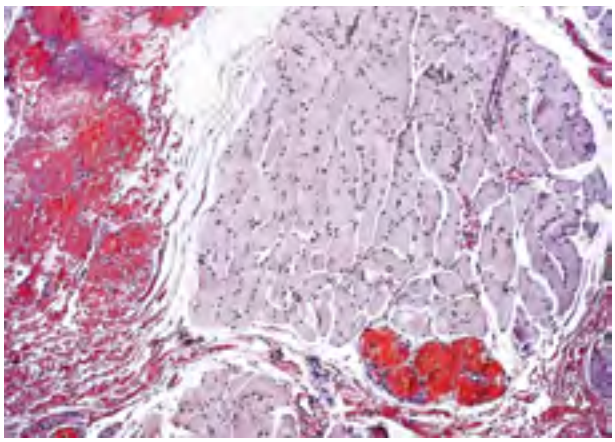

Fig. 4. Congo red stained section: positive staining in the amorphous deposits on the left and in the small fascicle with still preserved contours of the myocytes, on the right (original magnification 40×)

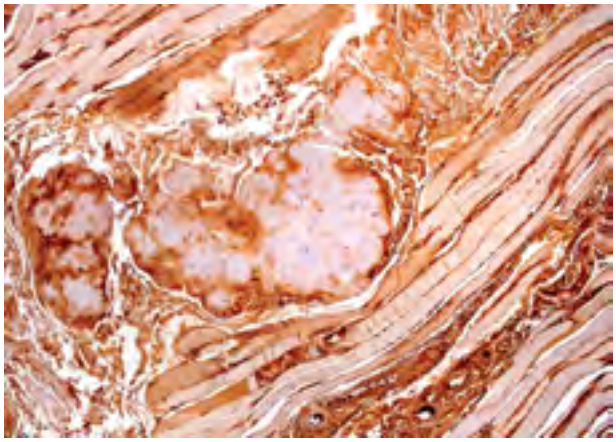

Fig. 5. Positive AL immunostaining in the homogenous deposits, in the endomysium (linear outer outlines of the fibres) and focally in the sarcoplasma (original magnification 40×)

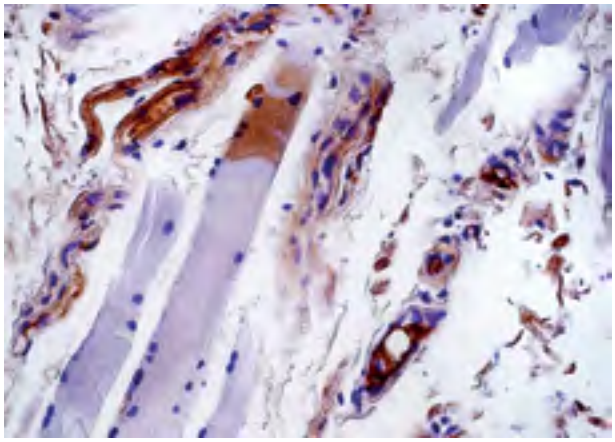

Fig. 6. Positive lambda light chain immunoreaction in vessel walls and intracellularly in the muscle fibre (original magnification 200×)

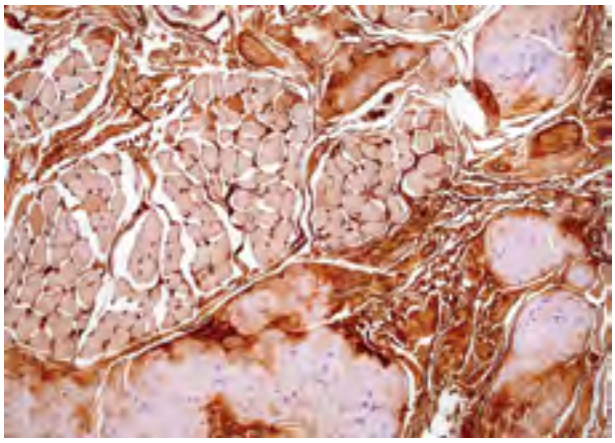

Fig. 7. Positive AL immunostaining in the rims of the deposits, in the perimysium, in two small nerve trunks and in the vessel walls (original magnification 40×)

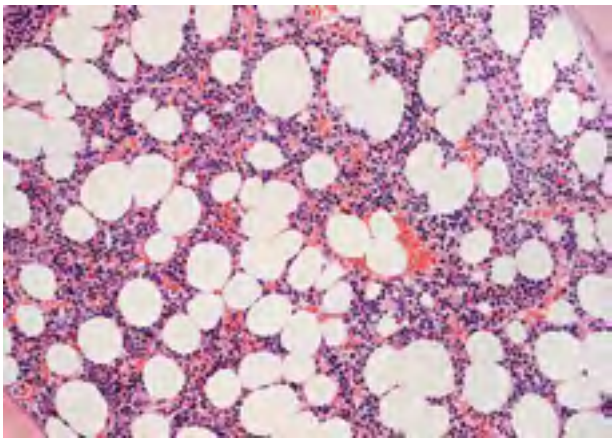

Fig. 8. The bone marrow biopsy with small aggregations of atypical plasma cells. HE

ed with systemic AL amyloidosis. The involvement of other than the tongue intra-oral tissues is generally considered as extremely rare [5]. We hereby present a case of oral manifestation of systemic AL amyloidosis with macroglossia and concomitant amyloid deposits in the buccal muscles with a unique microscopic presentation of amyloid fibrills localized intracellularly in striated muscles.

Clinical history and methods

A 59-year old Caucasian male was admitted to the Department of Periodontology and Oral Medicine with bilateral thickenings of buccal mucosa and dorsum of the tongue. The patient's past medical and dental histories were noncontributory. On admission his speech was slurred and he complained on xerostomia and dysphagia for solids. The patient reported frequent incidence of monocle hematomas after physical effort. Intraorally, a diffuse marble-like appearance of the buccal mucosa and dorsum of the tongue was observed, with accompanying submucosal thickenings on both cheeks, localized mainly around corners of the mouth. The thickened areas were stiff, hard, immobile and painless on palpation. There was also significant macroglossia with evident, deep indentations on the margins of the tongue and depapillation of its dorsum and reduced mobility (Figs. 1, 2).

The patient was reported to the Department of Oral Surgery where, under local anaesthesia, incisional biopsy of the buccal mucosa and underlying tissues was taken. Histopathological examination of the specimen revealed that the mucosa was separated from the muscle tissue with a layer of fibrous connective tissue with thickened, hyalinizing bands of collagen fibers among which numerous tiny aggregations of capillary vessels with thickening and homogenization of their walls were observed. In the muscular part of the specimen the abundant amorphous deposits dominated (Fig. 3). Those deposits were eosinophilic in HE sections and positive on Congo red staining with apple-green birefringence on polarisation, therefore, amyloid (Fig. 4). Furthermore, the central part of the deposits revealed calcifications, black on van Kossa staining. Amyloid seemed to replace completely some of the muscular fascicles. On cross section of the rest of the partially preserved muscles, the involvement of sarcoplasma was visible as the slightly eosinophilic areas without striations. The endomysial amyloid accumulation was well demonstrated on the longitudinal section, especially on AL immunostaining (Figs. 5, 6). Only a few blood vessels and small nerves in the perimysium showed congophilia and positive AL immunoreaction (Fig. 7). The diagnosis of AL amyloidosis was made with a suggestion for clinical investigation for plasma cell dyscrasia.

Accordingly, anterior-posterior and lateral X-rays of the skull and both femurs were performed but there were no radiographic features of lytic bone lesions. The patient was further reported to the Department of Hematology. On admission patient's general condition was average (Karnofsky grade 70, ECOG grade 2). On physical examination chronic right ventricular failure symptoms were revealed in the form of bilateral shanks oedema. The patient also suffered from dyspnea during moderate exertion due to left ventricular insufficiency. Over the heart apex a 2/6 systolic murmur was audible, otherwise particular parameters of the cardiovascular system were considered as normal.

Subsequently, the patient was subjected to bone marrow biopsy. Microscopically (Fig. 8) the bone marrow was considered as normocellular – cellularity varied from 40 to 60%. No abnormalities of marrow architecture were detected. Megakaryopoesis was considered as normal in number, size, shape and lobe configuration. There was no increase of immature

granulopoietic precursors and no dysgranulopoesis was evident. Erythroid clusters were correct in numbers and organization. About 15% of nucleated cells were atypical CD 138+ λ + plasma cells characterized with a diffuse pattern of infiltration (κ : λ ratio 1 : 15). Within periosteum and vessel walls, Congo red staining protein deposits positive in polarized light microscopic examination were identified. There was no increased fibrosis with only mild, patchy osteopenia. Primary amyloidosis/multiple myeloma – associated amyloidosis was diagnosed. The patient was scheduled for conventional cytostatic and high-dose chemotherapy supported by peripheral blood stem cell transplantation with CD34+ cell separation by G-CSF. However, due to the development of amyloid deposition in the blood vessels (with manifestations of skin and mucosal ecchymoses that present a significant predictor of pathological bleeding), vessels fragility and a reduced activity of thrombin and factor X which lose their function after binding with amyloid, massive bleeding into the central nervous system occurred. Before any systemic treatment was implemented, the patient died secondary to the damage of brain tissue, three months after diagnosis.

Discussion

The systemic light-chain amyloidosis (AL) is the most common type of systemic amyloidosis, has a slight male preponderance and an incidence of 8 to 10 cases per million person per year, with a median age at diagnosis of 63 and a median survival time, if left untreated, of 12 months [6]. It is characterized by a clonal population of plasma cells in the bone marrow that produce monoclonal light chain of kappa or lambda type. It is also the only type of amyloidosis associated with plasma cell dyscrasia and develops in approximately 15% of multiple myeloma patients [7].

It is widely recognized that amyloidosis involves the muscle tissue, especially myocardium, muscularis propriae and muscularis mucosa of the gastrointestinal tract as well as striated muscles of the tongue. Skeletal muscles may also be infiltrated with an unknown prevalence, mostly in systemic AL amyloidosis. The symptoms of amyloid myopathy include pseudohypertrophy, macroglossia, amyloidomas and – less frequently – progressive proximal weakness. Amyloid accumulates in perimysial connective tissue, predominantly around small blood vessels and less frequently in endomysium, sometimes encircling each muscle fibre. The changes in the perimysium and intramuscular blood vessels are sufficient to establish the diagnosis of the amyloid myopathy. Intracellular localization is unique: usually only minute sarcoplasmatic deposits are demonstrated in electron microscopy. The muscle abnormalities may be the first and only symptom of the disease. Amyloid myopathy is considered to be an underdiagnosed entity [8, 9, 10, 11, 12, 13]. In the presented case, the homogenous masses were undoubtedly considered to be amyloid; however, their localization in the striated muscles and the degree of involvement were unique. They might also correspond with an odd form of hyalinization or with the uric acid crystals destroyed by formalin fixation; nevertheless, green birefringence on polarisation of the Congo red positive sections confirmed amyloid deposits.

Once a diagnosis of accumulation of amyloid within the orofacial tissues is made, it is of vital importance to determine whether amyloid deposits represent localized or systemic amyloidosis, for there is a markedly shortened life expectancy in systemic forms of amyloidosis due to involvement of vital organs and excellent prognosis in the localized form [1, 14]. Oral manifestation of systemic amyloidosis mainly concerns the tongue. Amyloidosis of the tongue should be considered as a paraneoplastic manifestation of the underlying plasma cell dyscrasia, in particular myeloma [7].

The diagnostic workup scheme includes a full blood count, erythrocyte sedimentation rate, urea, creatinine, uric acid, calcium, albumin, alkaline phosphatase and immunoelectrophoretic examination of plasma and urine, followed by radiologic imaging series of the skeleton and a bone marrow biopsy [7]. Interrupting or at least limiting production of amyloid protein is the primary purpose of amyloidosis treatment. It leads to improvement of the organs efficiency that result in survival prolongation and its quality improvement.

In conclusion, we report a case of oral manifestation of AL amyloidosis with a very unique microscopic presentation of intracellular amyloid deposits in the buccal striated muscles. First manifestations of amyloidosis in the oral cavity may be vague and can mislead and delay the diagnosis and thus appropriate treatment.

The authors declare no conflict of interest.

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